TO TRACK HIV VACCINE RESEARCH AROUND THE WORLD, HAYNES KEEPS BOOKS OF DATA AND NOTES ON EACH MEETING AND PHONE CONVERSATION.
Bart Haynes combined his administrative genius and research acumen to create an investigative infrastructure like no other in medical science. CHAVI has organized big science and shifted the quest for an HIV/AIDS vaccine into overdrive.

COLLABORATION in a COMPETITIVE WORLD

BART HAYNES HAS THE FLU—in June, no less. It’s somewhat ironic that the man who directs the Duke Human Vaccine Institute, an organization dedicated to creating vaccines for HIV/AIDS, tuberculosis and influenza, finds himself struck down. “I even took the flu vaccine,” he says between sniffles. “We need to find a better one.”

Despite suffering from an unpleasant summer bug, Barton F. Haynes, MD, HS’73-’75, Duke’s Frederic M. Hanes Professor of Medicine and Immunology, has his gaze fixed firmly on HIV/AIDS, a disease for which no effective vaccine exists. The institute he established in 2005, the Center for HIV/AIDS Vaccine Immunology (CHAVI), is having a phenomenal year.

CHAVI has met the bold goal set by its founding seven-year, $300 million grant. Haynes and company determined how HIV/AIDS works in the human body and described why it is a much more difficult opponent than was first imagined. In July, the original CHAVI grantor, the National Institute of Allergy and Infectious Diseases, issued a second seven-year grant, this one for $140 million. The center’s name was changed to CHAVI-ID, with the new letters signifying Immunogen Discovery.

CHAVI-ID’s guiding purpose is to create a vaccine that can prevent initial HIV infection in humans. When CHAVI was first launched, investigators worldwide had no idea why time-tested techniques for vaccine development failed again and again with HIV. To answer that question, they had to learn their foe inside and out to figure out why the AIDS virus is so different from other pathogens. In the process, researchers made dozens of incremental advances that helped draw a detailed picture of their foe and, for the first time, define the rules of engagement.

BY GREG JENKINS
Haynes helped raise money to build this school, M’tendere Presbyterian, in Lusaka, Zambia

“Basically, in the last seven years we’ve come up with ways to deal with the diversity and the mutation of the virus,” Haynes says. “We know exactly what needs to be done...vaccine candidates and strategies are now being implemented and tried in nonhuman primates—Rhesus monkeys—and we’re also starting clinical trials to test the new generation of vaccines for their safety and for the types of protective immune responses they might induce.”

None of this work would have been possible—certainly not on this timeline—without a cry for change from within the HIV/AIDS research community, the ensuing bold steps taken by NIAID and the Bill and Melinda Gates Foundation, and Haynes’ creation of an entirely new investigative model that opened doors to a spirit of scientific collaboration.

Klausner, MD’77, G’03(hon.), issued a cry for help.

Their paper in the journal Science stated, essentially, that the field was going nowhere. They proposed a new collaborative investigative model that would increase resources, prioritize and speed up the pace of research, reduce redundancy, standardize candidate vaccine testing, expand manufacturing resources, and increase capacity for international clinical trials. The call was to create a global HIV vaccine enterprise that would end competition between researchers and get them working together.

NIAID and the Gates Foundation responded to this urgent plea with resources never seen before in HIV/AIDS research. NIAID funded CHAVI, while Gates funded the Collaboration for AIDS Vaccine Discovery (CAVD).

THE CALL WAS TO CREATE A GLOBAL HIV VACCINE ENTERPRISE THAT WOULD END COMPETITION BETWEEN RESEARCHERS AND GET THEM WORKING TOGETHER.

Now, the question was how to construct this brave new collaborative world. Haynes was well prepared to lead the charge on behalf of Duke, the five other research institutions in CHAVI, and the 92 organizations in 19 countries that made up the CAVD. He had a fully formed vision for the infrastructure that would bring the proposals of the Science paper to life. All it required was completely turning upside down the way research institutions and their staffs conduct themselves every day.

Haynes had four challenges in building his new model for research: 1) get everyone at CHAVI, from administrators to researchers, to buy in to the new model; 2) develop trust among the investigators so they felt safe sharing their data and ideas; 3) empower young investigators to work in teams but still pursue their own careers; and 4) make sure communication was enabled and encouraged.

The very first meeting of CHAVI in 2003 was a session in Durham that included 110 investigators recruited from around the world, NIH staff, and everyone’s administrators and financial people. “I said, ‘Everyone who thinks you’re going to help make this vaccine, stand up,’” Haynes says. “All the investigators stood up. And I said, ‘Now all of the administrators, and financial people, and grants people at NIH, you stand up.’ They all stood up. And I said, ‘The investigators won’t make a vaccine without you.’”

Haynes had realized earlier that one major problem with HIV research was that it moved so slowly that there would never be a vaccine in the lifetimes of the current researchers. CHAVI’s task was to move faster, and to move the investigators faster. Whenever a shared piece of information requiring action came to any staff member, the staffer was to move it forward with priority status. “The bottom line was that everyone in CHAVI was totally committed to the cause,” Haynes says.

“DON’T WORRY ABOUT GETTING FUNDED AGAIN...”

In 2003, Haynes was coming off an eight-year stint as chairman of Duke’s Department of Medicine to return to HIV research full-time. He and two dozen international HIV/AIDS research colleagues, including Richard D.
"It wasn’t just a job. That was a very important initial buy-in."

The concept of scientific secrecy, long held in a world where investigators and labs competed for precious and dwindling grant funding, took a bit longer to change. Some scientists didn’t embrace the new paradigm right away, and Haynes took immediate steps to correct their understanding. Soon, an environment blossomed where people felt comfortable talking about confidential information and new ideas and understood they were going to be allowed to pursue those ideas.

Tony Moody, MD, a B-cell immunologist and CHAVI’s chief medical officer, says he loves being able to talk to his colleagues about how his ideas might mesh with theirs and how they might work together to solve a problem. He describes this as a common, and very important, occurrence. “We all have the freedom to do that, and we have the trust of all of our other faculty and collaborators here,” Moody says. “That’s the most important aspect of the vaccine institute.”

CHAVI was an important lifeline to young investigators who otherwise might have been left to struggle in what Haynes and his colleagues agree is, outside of CHAVI, the worst NIH funding climate in decades. “We went out and recruited the brightest and the best, and provided an environment in which they could thrive. Not only survive, but thrive,” Haynes says. “They also were totally committed to the nature of the project. In addition to doing good science, they were committed to working on AIDS and making a difference on a societal problem. That’s very admirable.” The director is also proud that his vaccine institute has strived to make sure young investigators receive credit for the work that they do, and that they are encouraged to submit grants for their own research.

Ashley Trama, a talented PhD candidate in immunology, joined CHAVI because she had been involved in HIV research as an undergraduate, and she was looking for an outstanding mentor. “I would have a hard time working for five or six years on something with no relevance to humans and the greater good,” she says. “Working with Bart has been the perfect option for me in terms of mentorship, and on top of that, being able to study a virus that is so devastating.”

Haynes’ final concern in creating the structure for CHAVI was to ensure that within the team-based work and the expectations for continuous collaboration, researchers didn’t feel stifled. A constant stream of phone calls and e-mails made sure that teams moved forward and that the work was orchestrated so it could move as quickly as possible. But Haynes was careful that the structure didn’t stifle creativity. “We needed new discoveries to be made and new technologies to be developed,” he says. “We had to strike a balance between
ON THE TRAIL OF A CANDY COATED KILLER

In the last seven years, CHAVI investigators have learned an enormous amount about the nature of HIV and how it evades attempts to elicit an immune response. Haynes explains that when HIV research began 25 years ago, investigators thought they would take the envelope (the outer protein) of the virus, make it as a recombinant protein, and induce neutralizing antibodies. That process was used to make successful vaccines for Hepatitis B and countless other pathogens.

Researchers discovered that HIV is one of the world’s most rapidly mutating life forms, a survival strategy that enables it to easily evade the human immune response. The virus integrates into human DNA, a finding that changed the rules for how an HIV vaccine must be crafted. For diseases such as mumps or rubella, a vaccine can be effective even if a person is already infected at a low level. The vaccine causes a quick immune response to occur and eradicates the infection before the pathogen can take hold and cause clinical disease. The person is protected from disease, but not infection. That’s a perfectly acceptable emergency. It has been very gratifying clear to me that this was a humanitarian scientific project. At that time, it became been operating on a scale that this was a challenge of our time is inducement and camouflage. One bit of good news that helped focus research was the discovery by the CHAVI teams at Penn, Los Alamos, and Duke that although millions of strains of HIV exist in an infected person, in 80 percent of cases, only one virus is transmitted. This is the transmitted/founder virus, which quick became the main target of CHAVI’s research.

“With HIV, the rules are that we can’t allow someone to get infected, because once they’re infected, we can’t do anything about it,” Haynes says. “Once this bug goes into the host’s own genetic material, it becomes invisible to both antiretroviral drugs and to the immune system. That raises the bar considerably. We have to have what’s called sterilizing immunity. We have to be quite effective in preventing infection.”

But mutating by melding into human DNA is not HIV’s only trick. It also cloaks itself with a protective coating and camouflage. One bit of good news that allowed serendipity to occur.”

“CHAVI ... HAS BEEN A UNIQUE EXPERIENCE, AND SHOWED HOW TO WORK TOGETHER FOR BOTH GREAT SCIENCE AND THE GREATER GOOD.”

Bart Haynes

the virus envelope that would permit antibodies to bind there. Some of those spots are covered in sugar molecules to such an extreme degree that researchers refer to them as “candy coated,” and other spots look like human cells.

“The virus uses it as a perverse escape mechanism,” Haynes says. “The immune system is trained to not make responses against (human) cells, so as not to hurt ourselves and cause so-called autoimmune disease. It’s a very effective way of preventing the right response from being made.”

Further research by CHAVI and others found that there are some people who have been infected with HIV for long periods of time who begin to make the specialized antibodies that the body usually avoids making. Perhaps the immune system finally recognizes the invader and begins to fight it. Because the commonality of people living long lives after being infected with HIV is a relatively recent phenomenon, it took a while to discover this antibody production.

HOPE FROM THE OTHER SIDE OF THE WORLD

For many at CHAVI, the work of tackling perhaps the greatest global health challenge of our time is inducement enough to show up every day and do their best. For Haynes, there is a personal connection as well. He was confronted with the human toll of HIV/AIDS on his first trip to Africa in 2000, and later returned to Zambia, where he developed close friends and helped them raise funds to build a school. In the ensuing years, CHAVI developed a number of collaborator sites in Africa and Haynes returned several times.

“The need was just so profound,” he says. “Every family that I met had lost someone to AIDS. It was obvious that the vaccine was urgently needed. My lab, for the 10 years or so before that, had been operating on a scale that this was a scientific project. At that time, it became clear to me that this was a humanitarian emergency. It has been very gratifying
for me to meet and form a lot of good friendships with people in Africa, working relationships, and transferring a lot of the technology that we developed to Africa to try to build laboratories there to help young scientists there, to build the future.”

Inspiration also came in 2009 from the results of a vaccine trial on the other side of the world. The RV144 trial in Thailand tested a combination of two existing vaccines that had failed individually. RV144 was the first trial to produce evidence that an HIV vaccine was possible. Its efficacy rate of 31.2 percent was far short of being adequate for implementation, but it ignited a bonfire of follow-up studies. Researchers turned RV144 inside out to determine what made it modestly effective.

After two years analyzing samples from the Thai trial, a global team led by Haynes determined that IgG antibodies specific to a particular region of the HIV envelope called V1V2 was associated with lowered infection risk in trial participants, and IgA antibodies somehow led to greater infection risk—likely by interfering with potentially protective antibodies.

“That’s provided clues that we’re following to understand why RV144 worked, so the next vaccine can work better,” Haynes says.

That’s light years beyond where the HIV vaccine research field was seven years ago when CHAVI started. CHAVI’s success is the story of organizing big science and making it work for discovery. That’s an extremely rare occurrence, because big science is most often applied to technical problems. It becomes much harder when no one knows what the discovery will be.

“We had to organize to get specific tasks done, and for targeted creativity to solve specific problems on a basic science level,” Haynes says. “That was very difficult. We have now provided the methods for what we did to other groups who are forming consortia for discovery science. But basically, CHAVI has been a unique experience, and showed the way for how to work together for both great science and the greater good.”

**The CHAVI-ID team**

**IN A WORD,** the new CHAVI-ID will continue to be a collaboration, and collaboration among brilliant researchers has accelerated the pace of HIV/AIDS research in the past seven years and will continue to do so the next seven years. On a daily basis, investigators bounce ideas off one another, and samples are passed from lab to lab to extract different sets of data. CHAVI-ID is a complex web of teams and investigators working with other teams and investigators, supported by administrative and financial staff who keep track of data and make sure that the center stays compliant with the terms of the grant.

Center director Bart Haynes said that putting in place the support system for the investigators when CHAVI was originally formed was critical. The NIH’s grant conditions specified that 100 percent compliance was required, placing additional pressure on the fledgling research center to steward the money perfectly. If CHAVI couldn’t spend the money and get the work done, it would have been a disaster. Chief operating officer Tom Denny, along with associate director for finance Cherie Lahti and associate director for programs Kelly Soderberg, have kept CHAVI moving forward like the proverbial well-oiled machine.

“This team is the best team in the world at knowing how to administer large grants,” Haynes says. “When we got CHAVI, there had never been a research grant that size at Duke or anywhere. There was no one who could figure out how to administer such a grant—how to move that kind of money around in subcontracts. We had 110 subcontracts at any given time. It’s a massive effort, and our administration and our team had to learn it on the fly.”

**“WHEN WE GOT CHAVI, THERE HAD NEVER BEEN A RESEARCH GRANT THAT SIZE AT DUKE OR ANYWHERE.”**

Bart Haynes

Graduate student Ashley Trama and Professor Larry Liao in the CHAVI labs in MSRB II.

For more information on the CHAVI scientific team please see the complete list online at medalum.duke.edu.